APPENDIX A

Clean Version of Amended Claims

B4 1. (AMENDED) A catalytic antagonist of a target molecule, said antagonist comprising a targeting moiety, wherein said to said target molecule specifically binds to said targeting moiety, said targeting moiety being chemically attached to an enzyme, said enzyme being a hydrolase, that degrades said target molecule to reduce binding of the target molecule to its cognate ligand and to said targeting moiety thereby resulting in the release of said antagonist and thereby allowing said antagonist to bind and degrade another target molecule.

B5 6. (AMENDED) The antagonist of claim 1, wherein said hydrolase is selected from the group consisting of a protease, an esterase, an amidase, a lactamase, a cellulase, a lipase, a phospholipase, a phosphatase, a sulfatase, a lysozyme, a glycosidase, a nuclease, an aldolase, a ketolase, a lyase, a hyaluronidase, an amylase, a cerebrosidase and a chitinase.

B6 11. (AMENDED) The antagonist of claim 148, wherein said serine hydrolase is a chymotrypsin-type serine protease and said cysteine is substituted for the amino acid corresponding to a reference residue in a mature trypsin *Bos Taurus* (Protein Data Bank entry 1TPP), wherein said reference residue is at or near a residue selected from the group consisting of Tyr94, Leu99, Gln175, Asp189, Ser190, Gln192, Phe41, Lys60, Tyr151, Ser214, and Lys224.

B7 16. (AMENDED) The antagonist of claim 15, wherein said enzyme is a papain and said cysteine is substituted for the amino acid corresponding to a reference residue in a mature papain *Caraca Papaya* (Protein Data Bank entry 1BQI), where the reference residue is at or near a residue selected from the group consisting of Asn18, Ser21, Asn64, Tyr67, Trp69, Gln112, Gln142, Asp158, Trp177, and Phe207.

B8

18. (AMENDED) The antagonist of claim 17, wherein said enzyme is a metalloprotease and said cysteine is substituted for the amino acid corresponding to a reference residue in the mature human matrix metalloprotease MMP13 (Protein Data Bank entry 830C), where the reference residue is at or near a residue selected from the group consisting of Leu111, Phe175, Tyr176, Ser182, Leu184, Phe189, Tyr214, Asp231, Lys234, and Ile243.

19. (AMENDED) The antagonist of claim 1, wherein said target molecule is a molecule present on the surface of a cell.

B9

34. (AMENDED) The antagonist of claim 33, wherein the targeting moiety is a carbohydrate.

35. (AMENDED) The antagonist of claim 34, wherein said targeting moiety is thioethyl D-mannopyranoside.

B10

37. (AMENDED) A method of degrading a target molecule, said method comprising contacting said target molecule with a catalytic antagonist comprising a targeting moiety, wherein said target molecule specifically binds to said targeting moiety said targeting moiety being chemically attached to an enzyme, said enzyme being a hydrolase that degrades said target molecule resulting in the release of said antagonist thereby and allowing said antagonist to bind and degrade another target molecule.

B11

41. (AMENDED) The method of claim 37, wherein said hydrolase is selected from the group consisting of a protease, an esterase, an amidase, a lactamase, a cellulase, a lipase, a phospholipase, a phosphatase, a sulfatase, a lysozyme, a glycosidase, a nuclease, an aldolase, a ketolase, a lyase, a hyaluronidase, an amylase, a cerebrosidase and a chitinase.

B12

53. (AMENDED) The method of claim 52, wherein said enzyme is a papain and said cysteine is substituted for the amino acid corresponding to a reference residue in a mature *Caraca Papaya* papain (Protein Data Bank entry 1BQI)

B12 Cont selected from the group consisting of Asn18, Ser21, Asn64, Tyr67, Trp69, Gln112, Gln142, Asp158, Trp177, and Phe207.

55. (AMENDED) The method of claim 54, wherein said

B13 enzyme is a metalloprotease and said cysteine is substituted for the amino acid corresponding to a reference residue in the mature human matrix metalloprotease MMP13 (Protein Data Bank entry 830C).

59. (AMENDED) The method of claim 56, wherein said

B14 molecule present on the surface of a cell is a component of a cell wall.

60. (AMENDED) The method of claim 56, wherein said molecule present on the surface of a cell is a component of a cell membrane.

B15 72. (AMENDED) The method of claim 70, wherein said targeting moiety is thioethyl D-mannopyranoside.

~~146.~~ (CANCELED)

148. (AMENDED) The antagonist of claim 146, wherein said

B16 protease is a serine hydrolase.

~~153.~~ (CANCELED)

~~154.~~ (CANCELED)

155. The method of claim 42, wherein said protease is a serine

B17 hydrolase.

APPENDIX B

Amended Claims and Specification: with Markings To Show Changes Made

In the Claims:

1. (AMENDED) A catalytic antagonist of a target molecule, said antagonist comprising a targeting moiety [that specifically binds], wherein said to said target molecule specifically binds to said targeting moiety, said targeting moiety being chemically attached to an enzyme, said enzyme being a hydrolase, that degrades said target molecule to reduce binding of the target molecule to its cognate ligand and to said targeting moiety thereby resulting in the release of said antagonist and thereby allowing said antagonist to bind and degrade another target molecule.

6. (AMENDED) The antagonist of claim [147] 1, wherein said hydrolase is selected from the group consisting of a protease, an esterase, an amidase, a lactamase, a cellulase, a lipase, a phospholipase, a phosphatase, a sulfatase, a lysozyme, a glycosidase, a nuclease, an aldolase, a ketolase, a lyase, a hyaluronidase, an amylase, a cerebrosidase and a chitinase.

11. (AMENDED) The antagonist of claim 148, wherein said serine hydrolase is a chymotrypsin-type serine protease and said cysteine is substituted for the amino acid corresponding to a reference residue in a mature trypsin *Bos Taurus* (Protein Data Bank entry 1TPP), wherein said reference residue is at or near a residue selected from the group consisting of Tyr94, Leu99, Gln175, Asp189, Ser190, Gln192, Phe41, Lys60, Tyr151, Ser214, and Lys224.

16. (AMENDED) The antagonist of claim 15, wherein said enzyme is a papain and said cysteine is substituted for the amino acid corresponding to a reference residue in a mature papain *Caraca Papaya* (Protein Data Bank entry 1BQI), where the reference residue is at or near a residue selected from the group consisting of Asn18, Ser21, Asn64, Tyr67, Trp69, Gln112, Gln142, Asp158, Trp177, and Phe207.

18. (AMENDED) The antagonist of claim 17, wherein said enzyme is a metalloprotease and said cysteine is substituted for the amino acid corresponding to a reference residue in the mature human matrix metalloprotease MMP13 (Protein Data Bank entry 830C), where the reference residue is at or near a residue selected from the group consisting of Leu111, Phe175, Tyr176, Ser182, Leu184, Phe189, Tyr214, Asp231, Lys234, and Ile243.

19. (AMENDED) The antagonist of claim 1, wherein said target molecule is a molecule present on the surface of a cell.

34. (AMENDED) The antagonist of claim 33, wherein the targeting moiety is a carbohydrate.

35. (AMENDED) The antagonist of claim 34, wherein said targeting moiety is [-] thioethyl D-mannopyranoside.

37. (AMENDED) A method of degrading a target molecule, said method comprising contacting said target molecule with a catalytic antagonist comprising a targeting moiety [that specifically binds to], wherein said target molecule specifically binds to said targeting moiety said targeting moiety being chemically attached to an enzyme, said enzyme being a hydrolase that degrades said target molecule resulting in the release of said antagonist thereby and allowing said antagonist to bind and degrade another target molecule.

41. (AMENDED) The method of claim [154] 37, wherein said hydrolase is selected from the group consisting of a protease, an esterase, an amidase, a lactamase, a cellulase, a lipase, a phospholipase, a phosphatase, a sulfatase, a lysozyme, a glycosidase, a nuclease, an aldolase, a ketolase, a lyase, a hyaluronidase, an amylase, a cerebrosidase and a chitinase.

53. (AMENDED) The method of claim 52, wherein said enzyme is a papain and said cysteine is substituted for the amino acid corresponding to a reference residue in a mature *Caraca Papaya* papain (Protein Data Bank entry 1BQI)

selected from the group consisting of Asn18, Ser21, Asn64, Tyr67, Trp69, Gln112, Gln142, Asp158, Trp177, and Phe207.

55. (AMENDED) The method of claim 54, wherein said enzyme is a metalloprotease and said cysteine is substituted for the amino acid corresponding to a reference residue in the mature human matrix metalloprotease MMP13 (Protein Data Bank entry 830C), where the reference residue is at or near a residue selected from the group consisting of Leu111, Phe175, Tyr176, Ser182, Leu184, Phe189, Tyr214, Asp231, Lys234, and Ile243.

59. (AMENDED) The method of claim 56, wherein said molecule present on the surface of a cell is a component of a cell wall.

60. (AMENDED) The method of claim 56, wherein said molecule present on the surface of a cell is a component of a cell membrane.

72. (AMENDED) The method of claim 70, wherein said targeting moiety is [-] thioethyl D-mannopyranoside.

148. (AMENDED) The antagonist of claim [7] 146, wherein said protease is a serine hydrolase.

In the Specification:

Please replace the paragraph found at page 4, lines 9-14, with the following:

--In a particularly preferred embodiment the enzyme is a *Bacillus lentus* subtilisin (SBL). In preferred embodiments, the cysteine is substituted for an amino acid in a subtillisin, where the amino acid corresponds to a reference residue in a *Bacillus lentus* subtilisin, where the reference residue is at or near a residue selected from the group consisting of residue 156, residue 166, residue 217, residue 222, residue 62, residue 96, residue 104, residue 107, residue 189, and residue 209.--

Please replace the paragraph found at page 17, lines 27-28, with the following:

--Figure 24A, 14B, and 14C illustrate selective lectin degradation by sugar-modified Subtilisin-WT"referred to throughout this disclosure as "GG36-WT".--

Please replace the paragraph found at page 18, lines 5-6, with the following:

--Figure 19 is a plot of anti-biotin degredation by biotin-CMM as a function of time.--

APPENDIX C

Clean Version of All Pending Claims and Specification

In the Claims:

1. (AMENDED) A catalytic antagonist of a target molecule, said antagonist comprising a targeting moiety, wherein said to said target molecule specifically binds to said targeting moiety, said targeting moiety being chemically attached to an enzyme, said enzyme being a hydrolase, that degrades said target molecule to reduce binding of the target molecule to its cognate ligand and to said targeting moiety thereby resulting in the release of said antagonist and thereby allowing said antagonist to bind and degrade another target molecule.

2. The antagonist of claim 1, wherein said targeting moiety is joined to said enzyme through the sulfur group on a cysteine.

3. The antagonist of claim 2, wherein said cysteine is a cysteine that is substituted for a native amino acid other than cysteine in said enzyme.

4. The antagonist of claim 3, wherein said cysteine is a cysteine that is substituted for a native amino acid other than cysteine in or near a subsite comprising a substrate binding site of said enzyme.

5. The antagonist of claim 4, wherein said cysteine is a cysteine that is substituted for an amino acid forming a substrate binding site.

6. (AMENDED) The antagonist of claim 1, wherein said hydrolase is selected from the group consisting of a protease, an esterase, an amidase, a lactamase, a cellulase, a lipase, a phospholipase, a phosphatase, a sulfatase, a lysozyme, a glycosidase, a nuclease, an aldolase, a ketolase, a lyase, a hyaluronidase, an amylase, a cerebrosidase and a chitinase.

7. The antagonist of claim 6, wherein said hydrolase is a protease.

8. The antagonist of claim 149, wherein said serine hydrolase is a subtilisin-type serine hydrolase and said cysteine is substituted for an amino acid in or near a subsite selected from the group consisting of an S1 subsite, an S1' subsite, and an S2 subsite.

9. The antagonist of claim 8, wherein said enzyme is a *Bacillus lentus* subtilisin.

10. The antagonist of claim 8, wherein said cysteine is substituted for an amino acid corresponding to a reference residue in a *Bacillus lentus* subtilisin, where said reference residue is at or near a residue selected from the group consisting of residue 156, residue 166, residue 217, residue 222, residue 62, residue 96, residue 104, residue 107, residue 189, and residue 209.

11. (AMENDED) The antagonist of claim 148, wherein said serine hydrolase is a chymotrypsin-type serine protease and said cysteine is substituted for the amino acid corresponding to a reference residue in a mature trypsin *Bos Taurus* (Protein Data Bank entry 1TPP), wherein said reference residue is at or near a residue selected from the group consisting of Tyr94, Leu99, Gln175, Asp189, Ser190, Gln192, Phe41, Lys60, Tyr151, Ser214, and Lys224.

12. The antagonist of claim 148, wherein said serine hydrolase is an alpha/beta type serine hydrolase and said cysteine is substituted for the amino acid corresponding to a reference residue in a *Candida antartica* lipase (Protein Data Bank entry 1TCA), where the reference residue is at or near a residue selected from the group consisting of Trp104, Leu140, Leu144, Val154, Glu188, Ala 225, Leu278 and Ile285.

13. The antagonist of claim 7, wherein said enzyme is an aspartyl protease.

14. The antagonist of claim 13, wherein said enzyme is a pepsin-type protease and said cysteine is substituted for the amino acid corresponding to a reference residue in the mature human pepsin (Protein Data Bank entry 1PSN), where the reference residue is at or near a residue selected from the group consisting of Tyr9, Met12, Glu13, Gly76, Thr77, Phe111, Phe117, Ile128, Ser130, Tyr189, Ile213, Glu239, Met245, Gln287, Met289, Leu291, and Glu294.

15. The antagonist of claim 7, wherein said enzyme is a cysteine protease.

16. (AMENDED) The antagonist of claim 15, wherein said enzyme is a papain and said cysteine is substituted for the amino acid corresponding to a reference residue in a mature papain *Caraca Papaya* (Protein Data Bank entry 1BQI), where the reference residue is at or near a residue selected from the group consisting of Asn18, Ser21, Asn64, Tyr67, Trp69, Gln112, Gln142, Asp158, Trp177, and Phe207.

17. The antagonist of claim 7, wherein said enzyme is a metalloprotease.

18. (AMENDED) The antagonist of claim 17, wherein said enzyme is a metalloprotease and said cysteine is substituted for the amino acid corresponding to a reference residue in the mature human matrix metalloprotease MMP13 (Protein Data Bank entry 830C), where the reference residue is at or near a residue selected from the group consisting of Leu111, Phe175, Tyr176, Ser182, Leu184, Phe189, Tyr214, Asp231, Lys234, and Ile243.

19. (AMENDED) The antagonist of claim 1, wherein said target molecule is a molecule present on the surface of a cell.

20. The antagonist of claim 19, wherein said molecule present on the surface of a cell is a molecule forming a receptor.

21. The antagonist of claim 19, wherein said molecule present on the surface of a cell is a ligand.

22. The antagonist of claim 19, wherein said molecule present on the surface of a cell is a component of a cell wall.

23. The antagonist of claim 19, wherein said molecule present on the surface of a cell is a component of a cell membrane.

24. The antagonist of claim 1, wherein said targeting moiety is selected from the group consisting of a protein, an antigen , a carbohydrate, a nucleic acid, a lipid, a coordination complex, a sugar, a vitamin, a dendrimer, and a crown ether.

25. The antagonist of claim 24, wherein said targeting moiety is a cognate ligand for a receptor or an enzyme.

26. The antagonist of claim 24, wherein said targeting moiety is an inhibitor for a receptor or an enzyme.

27. The antagonist of claim 1, wherein said enzyme is a protease and said targeting moiety is a ligand selected from the group consisting of a carbohydrate, a vitamin or vitamin analog, an enzyme inhibitor, a peptide, a pharmaceutical that is a small organic molecule, and biotin.

28. The antagonist of claim 1, wherein said enzyme is a protease and said targeting moiety is a receptor.

29. The antagonist of claim 27, wherein said enzyme is a subtilisin.

30. The antagonist of claim 29, wherein said targeting moiety is an enzyme inhibitor that is a pyrazole.

31. The antagonist of claim 29, wherein said targeting moiety is a biotin.

32. The antagonist of claim 29, wherein said targeting moiety is a ligand that binds a lectin.

33. The antagonist of claim 32, wherein said lectin is concanavalin A.

34. (AMENDED) The antagonist of claim 33, wherein the targeting moiety is a carbohydrate.

35. (AMENDED) The antagonist of claim 34, wherein said targeting moiety is thioethyl D-mannopyranoside.

36. The antagonist of claim 33, wherein said targeting moiety specifically binds to a soil and said enzyme degrades a component of said soil.

37. (AMENDED) A method of degrading a target molecule, said method comprising contacting said target molecule with a catalytic antagonist comprising a targeting moiety, wherein said target molecule specifically binds to said targeting moiety said targeting moiety being chemically attached to an enzyme, said enzyme being a hydrolase that degrades said target molecule resulting in the release of said antagonist thereby and allowing said antagonist to bind and degrade another target molecule.

38. The method of claim 37, wherein said targeting moiety is joined to said enzyme through the sulfur group on a cysteine.

39. The method of claim 38, wherein said cysteine is a cysteine that is substituted for a native amino acid other than cysteine in said enzyme.

40. The method of claim 39, wherein said cysteine is a cysteine that is substituted for a native amino acid other than cysteine in or near a subsite comprising a substrate binding site of said enzyme.

41. (AMENDED) The method of claim 37, wherein said hydrolase is selected from the group consisting of a protease, an esterase, an amidase, a lactamase, a cellulase, a lipase, a phospholipase, a phosphatase, a sulfatase, a lysozyme, a glycosidase, a nuclease, an aldolase, a ketolase, a lyase, a hyaluronidase, an amylase, a cerebrosidase and a chitinase.

42. The method of claim 41, wherein said hydrolase is a protease.

43. The method of claim 155, wherein said serine hydrolase is a subtilisin.

44. The method of claim 40, wherein said cysteine is a cysteine that is substituted for an amino acid forming a substrate binding site.

45. The method of claim 43, wherein said serine hydrolase is a subtilisin-type serine hydrolase and said cysteine is substituted for an amino acid in or near a subsite selected from the group consisting of an S1 subsite, an S1' subsite, and an S2 subsite.

46. The method of claim 43, wherein said subtilisin is a *Bacillus lentus* subtilisin.

47. The method of claim 45, wherein said cysteine is substituted for an amino acid corresponding to a reference residue in a *Bacillus lentus* subtilisin, where said reference residue is at or near a residue selected from the group consisting of residue 156, residue 166, residue 217, residue 222, residue 62, residue 96, residue 104, residue 107, residue 189, and residue 209.

48. The method of claim 155, wherein said serine hydrolase is a chymotrypsin-type serine protease and said cysteine is substituted for an amino acid corresponding to a reference residue in a mature trypsin (Protein Data Bank entry 1TPP), wherein said reference residue is at or near a residue selected from the group consisting of Tyr94, Leu99, Gln175, Asp189, Ser190, Gln192, Phe41, Lys60, Tyr151, Ser214, and Lys224.

49. The method of claim 155, wherein said serine hydrolase is an alpha/beta type serine hydrolase and said cysteine is substituted for an amino acid corresponding to a reference residue in a *Candida antartica* lipase (Protein Data Bank entry 1TCA), where the reference residue is at or near a residue selected from the

group consisting of Trp104, Leu140, Leu144, Val154, Glu188, Ala 225, Leu278 and Ile285.

50. The method of claim 42, wherein said enzyme is an aspartyl protease.

51. The method of claim 50, wherein said enzyme is a pepsin-type protease and said cysteine is substituted for the amino acid corresponding to a reference residue in the mature human pepsin (Protein Data Bank entry 1PSN), where the reference residue is at or near a residue selected from the group consisting of Tyr9, Met12, Glu13, Gly76, Thr77, Phe111, Phe117, Ile128, Ser130, Tyr189, Ile213, Glu239, Met245, Gln287, Met289, Leu291, and Glu294.

52. The method of claim 42, wherein said enzyme is an cysteine protease.

53. (AMENDED) The method of claim 52, wherein said enzyme is a papain and said cysteine is substituted for the amino acid corresponding to a reference residue in a mature *Caraca Papaya* papain (Protein Data Bank entry 1BQI) selected from the group consisting of Asn18, Ser21, Asn64, Tyr67, Trp69, Gln112, Gln142, Asp158, Trp177, and Phe207.

54. The method of claim 42, wherein said enzyme is a metalloprotease.

55. (AMENDED) The method of claim 54, wherein said enzyme is a metalloprotease and said cysteine is substituted for the amino acid corresponding to a reference residue in the mature human matrix metalloprotease MMP13 (Protein Data Bank entry 830C), where the reference residue is at or near a residue selected from the group consisting of Leu111, Phe175, Tyr176, Ser182, Leu184, Phe189, Tyr214, Asp231, Lys234, and Ile243.

56. The method of claim 37, wherein said target is a molecule present on the surface of a cell.

57. The method of claim 56, wherein said molecule present on the surface of a cell is a molecule forming a receptor.

58. The method of claim 56, wherein said molecule present on the surface of a cell is a ligand.

59. (AMENDED) The method of claim 56, wherein said molecule present on the surface of a cell is a component of a cell wall.

60. (AMENDED) The method of claim 56, wherein said molecule present on the surface of a cell is a component of a cell membrane.

61. The method of claim 37, wherein said targeting moiety is selected from the group consisting of a protein, an antigen, a carbohydrate, a nucleic acid, a lipid, a coordination complex, a sugar, a vitamin, a dendrimer, and a crown ether.

62. The method of claim 61, wherein said targeting moiety is a cognate ligand for a receptor or an enzyme.

63. The method of claim 61, wherein said targeting moiety is an inhibitor for a receptor or an enzyme.

64. The method of claim 37, wherein said enzyme is a protease and said targeting moiety is a ligand selected from the group consisting of a carbohydrate, a vitamin or vitamin analog, an enzyme inhibitor, a peptide, a pharmaceutical that is a small organic molecule, and biotin.

65. The method of claim 37, wherein said enzyme is a protease and said targeting moiety is a receptor.

66. The method of claim 64, wherein said enzyme is a subtilisin.

67. The method of claim 66, wherein said targeting moiety is an enzyme inhibitor that is a pyrazole.

68. The method of claim 66, wherein said targeting moiety is an biotin.

69. The method of claim 66, wherein said targeting moiety is a ligand that binds a lectin.

70. The method of claim 69, wherein said lectin is concanavalin A.

71. The method of claim 70, wherein targeting moiety is a carbohydrate.

72. (AMENDED) The method of claim 70, wherein said targeting moiety is thioethyl D-mannopyranoside.

73. The method of claim 66, wherein said targeting moiety specifically binds to a soil and said enzyme degrades a component of said soil.

148. (AMENDED) The antagonist of claim 146, wherein said protease is a serine hydrolase.

149. The antagonist of claim 148, where said serine hydrolase is a subtilisin-type serine hydrolase.

155. The method of claim 42, wherein said protease is a serine hydrolase.

In the Specification:

Please replace the paragraph found at page 4, lines 9-14, with the following:

—In a particularly preferred embodiment the enzyme is a *Bacillus lentus* subtilisin (SBL). In preferred embodiments, the cysteine is substituted for an amino acid in a subtillisin, where the amino acid corresponds to a reference residue in a *Bacillus lentus* subtilisin, where the reference residue is at or near a residue selected from the group

consisting of residue 156, residue 166, residue 217, residue 222, residue 62, residue 96, residue 104, residue 107, residue 189, and residue 209.–

Please replace the paragraph found at page 17, lines 27-28, with the following:

Figure 34A, 14B, and 14C illustrate selective lectin degradation by sugar-modified Subtilisin-WT" referred to throughout this disclosure as "GG36-WT".

Please replace the paragraph found at page 18, lines 5-6, with the following:

Figure 19 is a plot of anti-biotin degredation by biotin-CMM as a function of time.